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(54) Title: METHOD AND COMPOSITION FOR REMOVAL OF MERCURY RELEASED FROM AMALGAM IN THE ORAL CAVITY

(57) Abstract

A method for removal from the oral cavity of elementary mercury (Hg^0) released from amalgam in dental fillings affected by mechanical means, such as drills and other abrasive tools comprises administration to the oral cavity of the patient being treated of an effective amount of an agent having high affinity for mercury ion (Hg^{2+}), such as EDTA or a sodium or potassium salt of EDTA. Also disclosed is an aqueous composition for use in the method which may comprise a viscosity-increasing agent, and the use of said agent for the manufacture of a medicament for prevention of Hg^0 uptake by the human body.

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Method and composition for removal of mercury released from amalgam in the oral cavity

FIELD OF THE INVENTION

The invention relates to a method for removal from the oral cavity of elementary mercury (Hg^0) released from amalgam in dental fillings affected by mechanical means, such as drills and other abrasive tools. The invention also relates to a composition for use in such method and to the its preparation.

BACKGROUND OF THE INVENTION

Amalgam has been used in dentistry for over 80 years. It is estimated that about 10 million amalgam fillings per day were put into place during the period from the mid-1950s to the about 1980. Since then, the use of amalgam in dentistry has been a matter of heated debate. Dental amalgam consists of mercury, silver, tin, copper and zinc; it is obtained by mixing mercury with an alloy consisting of the other elements. The mercury content of amalgam ranges from 50 to 60%. Dental amalgam forms a plastic mass which easily may be filled into a prepared tooth cavity. The health hazard associated with potential endogenous accumulation of mercury has been recognized. Exposure to mercury may be due to slow continuous emission of mercury vapour from amalgam fillings (Stock A, *Die Gefährlichkeit des Quecksilber-dampfes und der Amalgame*. Z. Angew. Chemie. 1926 39:984-9). In addition, considerable exposure to mercury has been observed in association with insertion and removal of amalgam fillings leading to absorption as indicated by high concentrations of mercury in urine (Frykholm K O, *Mercury from dental amalgam, its toxic and allergic effects and some comments on occupational hygiene*. Acta Odontol. Scand. 1957:15, suppl. 22:1-108).

Recent studies have verified these early observations. Mercury vapour (Hg^0) has been detected in the oral cavity of individuals with amalgam fillings. Its release from the occlusal surfaces of fillings is accelerated by a variety of mechanical actions on the amalgam. Such actions involve insertion, remodelling, polishing, chewing, brushing and removal of fillings. Oral breathing sweeps the vapour into the respiratory passages resulting in pulmonary absorption. Some mercury vapour might also diffuse through the tissues lining the oral cavity and enter the blood stream. In addition the vapour may be dissolved in saliva and be oxidized to divalent inorganic mercury (Hg^{2+}). Hydrogen peroxide, often present on the surfaces of oral tissues due to bacteria, may be involved in the oxidation process. Inhaled mercury vapour is completely absorbed across the pulmonary membranes resulting in a net retention of about 80% of the inhaled dose. At least 50% of the retained vapour passes across the alveolar membranes directly into the blood stream where it dissolves in plasma and is distributed to all tissues in the body. In view of its lipid solubility, the dissolved vapour penetrates cell membranes, the blood brain barrier, and the placenta without hindrance. Once inside cells Hg^0 is oxidised to Hg^{2+}. The latter is released from cells and tissues, and eventually redistributes, primarily to the kidneys. A main difference in disposition between inhaled Hg-vapour and the ingested (saliva bound) inorganic mercury is the far greater brain uptake and placental transport following vapour inhalation.

Metallic mercury vapour is highly toxic. Distinct effects on the central nervous system, lungs and the renal system may be demonstrated after exposure corresponding to average urinary mercury concentrations of 20-50 ng per inhalation. Acute exposure to high concentrations of mercury vapour causes pneumonitis. The classical effects of chronic poisoning present as mental changes, tremor, gingivitis,

nephritis and allergic dermatitis. Knowledge concerning carcinogenic effects of inorganic mercury is incomplete. Some epidemiological data suggest an increased risk for tumour development in subjects exposed to mercury.

The amount of mercury released from permanent amalgam fillings is unknown. A growing number of amalgam bearers claim a number of symptoms caused by amalgam, often in direct connection with insertion or removal of fillings. Amalgam fillings thus constitute a serious health problem. Consequently, health authorities in various countries are considering a general ban on the use of amalgam in dentistry.

Although a sharp reduction in amalgam use may be anticipated in the future, millions of individuals are already bearers of amalgam fillings. Removal of their fillings to reduce mercury exposure is commonly performed today. Removal of amalgam fillings, however, involves steps in which substantial quantities of mercury vapour are released into the oral cavity, and thereby become available for inhalation. Moreover, polishing procedures of permanent amalgam fillings also result in the release of mercury vapour. Mechanical handling of intra-oral fillings and repair material resulting in heating of amalgam may further contribute to mercury release. Consequently, removal of dental fillings has been shown to cause a considerable increase in urinary mercury.

OBJECTS OF THE INVENTION

There are no efficient techniques described in literature or in clinical use for reducing the background evaporation of mercury from amalgam fillings. However, certain measures are sometimes undertaken in clinical dental health care in order to limit the release of mercury or the uptake of mercury by the patient and/or by dental health care personnel.

One such method is the cofferdam technique for enclosing the area of the dental filling selected for drilling or similar measures. A soft and elastic plastic material is placed around a single tooth and can be stretched to more or less cover the cavity formed during removal of amalgam or prepared in a tooth for filling with amalgam. This plastic material has been developed for use in endodontic root canal treatment. It may limit the swallowing of amalgam fragments and possibly also of saliva carrying dissolved mercury or finely dispersed amalgam fragments. The cofferdam technique, however, does not provide protection against mercury vapour which is freely released into surrounding air for subsequent inhalation.

Another method in use is intraoral suction which may have a similar effect as that of the cofferdam technique. The total content of saliva-born mercury may be reduced at any given time although gingival contact of remaining saliva still is likely to permit direct absorption through the mucosa of divalent metallic mercury. The suction per se may result in a certain removal, however incomplete, of mercury vapour from the oral cavity. This technique requires assistance by personnel or devices applied around the tooth which limit the intra oral spread of mercury-contaminated water from high speed drilling devices or instruments used for polishing.

A further method in use is cooling and water flushing of the amalgam material during mechanical working by drills, abrasives, etc., leading to an increase in temperature of the amalgam and thus indreased mercury release. Various cooling techniques are known in the art. Efficient cooling necessitates the adduction of substantial volumes of cooling medium which has to be continuously removed from the oral cavity, a problem for which there is no adequate solution.

Extra oral suction and external ventilation will reduce the exposure of dental health care personnel to mercury vapour. This technique requires the use of face masks and is expensive and cumbersome. Moreover, it does not protect the patient.

EP-B1 0 262 970 discloses a composition for absorbing mercury vapour formed from dental amalgam, comprising an iodide, a polyhydric alcohol, and a Lewis acid. For reasons of toxicity this known composition does not seem to be useful for application in the oral cavity of a patient. Similar compositions of this kind employing thiosulfate ion are also known, for instance from GB-A 2 122 916.

Consequently, none of the presently used methods simply and efficiently reduces access of mercury vapour released from amalgam to the airways.

It is thus a prime object of the invention to reduce the uptake by the human body of mercury vapour present in the oral cavity, in particular in connection with the working of amalgam in dentistry.

SUMMARY OF THE INVENTION

According to the present invention there is provided a method for limiting the uptake of mercury vapour by the airways of a patient being treated in dental care and having amalgam fillings.

The method according to the invention comprises administration to the oral cavity of the patient being treated of an effective amount of an agent having high affinity for mercury ion (Hg^{2+}), in the present context also called mercury scavenging agent.

Particularly preferred is EDTA (ethylenediamine

tetraacetic acid) or suitable pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts, preferably in form of an aqueous solution thereof. Also preferred is EGTA, cysteine, 2,3-dimercaptopropane-1-sulphonate (DMPS), D-penicillamine, meso-2,3-dimercaptosuccinic acid (DMSA), N-acetyl-D,L-penicillamine (NAP), dimercaprol, EDTA-sodium, EDTA- disodium, EDTA-trisodium, EDTA-calcium disodium, 2,3,dimercaptopropane-1-sulphonate, 2,3-dimercaptosuccinic acid, deferoxamine, ditiocarbamate sodium, aluminum salts, sodium citrate, sodium glucuronate, tartaric acid or its sodium and potassium salts, sodium hexametaphosphate, acidic sodium pyrophosphate, sodium tripolyphosphate, anthranilic acid, phosphonate, polyacrylic acid, alkyl-diamine polyacetic acids and their salts, pentetic acid, succimer and trientine.

It is preferred to feed the solution of said agent into the oral cavity of the patient in increments or continuously, and to remove it therefrom by suction or by rinsing in increments. The application of the solution into the oral cavity may be achieved by several different means. In its simplest form administration may be achieved by direct flushing by means of a syringe during the dental procedure. It may also be administered by pre-soaked woven or non-woven tissue or some other type of scavenging agent reservoir being placed in close proximity of the intra-oral area where mercury emission is expected to occur. Such tissue may be based on paper or cotton swabs, etc. Other application methods make use of a pumping device for pumping the solution into the oral cavity at a slow rate or of passive flow of said solution administered directly via the drilling equipment (the drill head) in close proximity of the drill. Similar designs may be used for administration during procedures other than drilling, e.g., during polishing of amalgam materials or during filling or application of amalgam in the oral cavity. Reservoirs for

the mercury-scavenging agents of the invention may also be applied at the rim of fixed suction devices in the oral cavity. Such devices comprise Clean Up (registered trade mark of AGDA gruppen AB, Orsa, Sweden). Other devices that may be used include cups fixed around one or several teeth in order to create a basin which may be filled with the agent according to the invention, thereby completely covering the amalgam surface during the drilling or polishing procedure.

According to the present invention there is also provided an aqueous composition for use in said method, comprising EDTA or a pharmacologically acceptable salt thereof, in particular an alkali salt such as a sodium, potassium or calcium salt, dissolved in an appropriate amount of water or other suitable aqueous medium to make-up a solution containing from 0,01 % by weight to 5 % by weight of EDTA or said pharmacologically acceptable EDTA salt. The composition according to the invention may also contain agents increasing its viscosity, such as carrageenan or carboxymethyl cellulose, and agents improving its taste, such as peppermint oil or spearmint oil. It is also preferred to substitute EDTA by one or several agents selected from the group EGTA, cysteine, 2,3-dimercapto-propane-1-sulphonate (DMPS), D-penicillamine, meso-2,3-dimercaptosuccinic acid (DMSA), N-acethyl-D-L-penicillamine (NAP), dimercaprol, and diethyldithiocarbamate. It is furthermore preferred to set the pH of the aqueous composition according to the invention by adding a pharmacologically acceptable acid, such as phosphoric acid or an acidic salt thereof, a pharmacologically acceptable base, such as sodium hydroxide, or a weak salt thereof, such as sodium carbonate or sodium bicarbonate, or by adding a suitable buffering agent, such as a combination of sodium dihydrogen phosphate and disodium hydrogen phosphate. Preferably the pH of the aqueous composition will be from 5.0 to 8.5, preferably from 6 to 7.5.

According to the present invention is also disclosed the use of an agent for scavenging mercury in an ionic state to prevent uptake of mercury in an atomic state by the human body for the manufacture of a medicament for the prevention of Hg^0 uptake by the human body. Agents, carriers, and additives useful in this context are mentioned above in connection with the composition according to the invention.

The method according to the invention is surprisingly effective in reducing the concentration of mercury vapour in the oral cavity of a patient. EDTA is only known to strongly complex mercury ion whereas it is effective, according to the invention, to substantially reduce elementary mercury (Hg^0) present in the oral cavity of a patient. An survey of the accumulation and biotransfer of mercury is given by M Nylander in *Accumulation and Biotransformation of Mercury and its Relationship to Selenium after Exposure to Inorganic Mercury and Methyl Mercury. A Study on Individuals with Amalgam Fillings, Dental Personnel, and Monkeys*. Thesis, Dept. Of Environmental Hygiene and Inst. of Environmental Medicine, Karolinska Institutet, Stockholm 1990.

The invention will be better understood by a preferred embodiment described in the following in form of an example.

DESCRIPTION OF A PREFERRED EMBODIMENT

Example

In order to test the invention standardized cavities (diameter 3mm) were prepared by means of a high-speed drill in acrylic teeth shaped and sized similar to human teeth. The cavities were filled with dental amalgam (non-gamma two amalgam) which was allowed to set for at least 24 hours. A plastic cylindrical sphere with a volume of 300 ml and an

oval opening (4x5 cm) was used to simulate the oral cavity. The acrylic teeth filled with amalgam were fixed, one for each experiment, by a screwing device inside the lower half of the artificial oral cavity. A solution containing 2.0 mg/ml EDTA in sterile water (pH=7) was prepared and applied by a syringe connected to an infusion pump for constant fluid perfusion at a speed of 1.00 ml/minute. The amalgam was removed by an experienced dentist using a regular dental high-speed drilling device and a sharp bur. Special attention was given to removing each filling in approximately 60 seconds which would correspond to a clinically acceptable and commonly used rate. The EDTA solution was continuously flushed over the amalgam filling during the drilling procedure via a needle inserted through the plastic cavity wall.

Accumulated mercury vapour, Hg^0, was measured once every 5 seconds via a probe placed immediately in front of the "cavity" and connected to a Hg analyser (JEROME 411). Experiments were repeated after cleaning each tooth from amalgam. EDTA solution and water were given randomly in a fashion blinded to the dentist performing the drilling. The concentration of mercury vapour, Hg^0, expressed as $\mu g/m^3$ during 60 seconds of drilling in 4 plus 4 experiments is shown in Figure 1.

As shown by the results in Fig. 1 the mean "intra oral" concentration of mercury vapour was reduced 4-8 fold during the drilling procedure in presence of EDTA in the flush solution. The calculated accumulated release of mercury vapour during 60 seconds of drilling was reduced from 3152 to 750 $\mu g/m^3$ at average.

Claims

1. A method for removal from the oral cavity of elementary mercury (Hg^0) released from amalgam in dental fillings affected by mechanical means, such as drills and other abrasive tools, characterized by administration to the oral cavity of the patient being treated of an effective amount of an agent having high affinity for mercury ion (Hg^{2+}).

2. The method of claim 1, characterized in that said agent is EDTA (ethylenediamine tetraacetic acid) or a suitable pharmaceutically acceptable salts thereof, such as a sodium, potassium or calcium salt.

3. The method of claim 1, characterized in that said agent is EGTA, cysteine, 2,3-dimercaptopropane-1-sulphonate (DMPS), D-penicillamine, meso-2,3-dimercaptosuccinic acid (DMSA), N-acetyl-D-L-penicillamine (NAP), dimercaprol, and diethyldithiocarbamate.

4. The method of any of claims 1-3, characterized in that said agent is dissolved in an aqueous carrier which is fed continuously or in increments into the oral cavity.

5. The method of any of claims 1-3, characterized in that said agent is contained in an absorptive material for disposition in the oral cavity.

6. An aqueous composition for scavenging elementary mercury in the oral cavity, comprising an scavenging-effective amount of EDTA or an alkali salt of EDTA dissolved in an aqueous carrier to a concentration of from 0,01 % by weight to 5 % by weight.

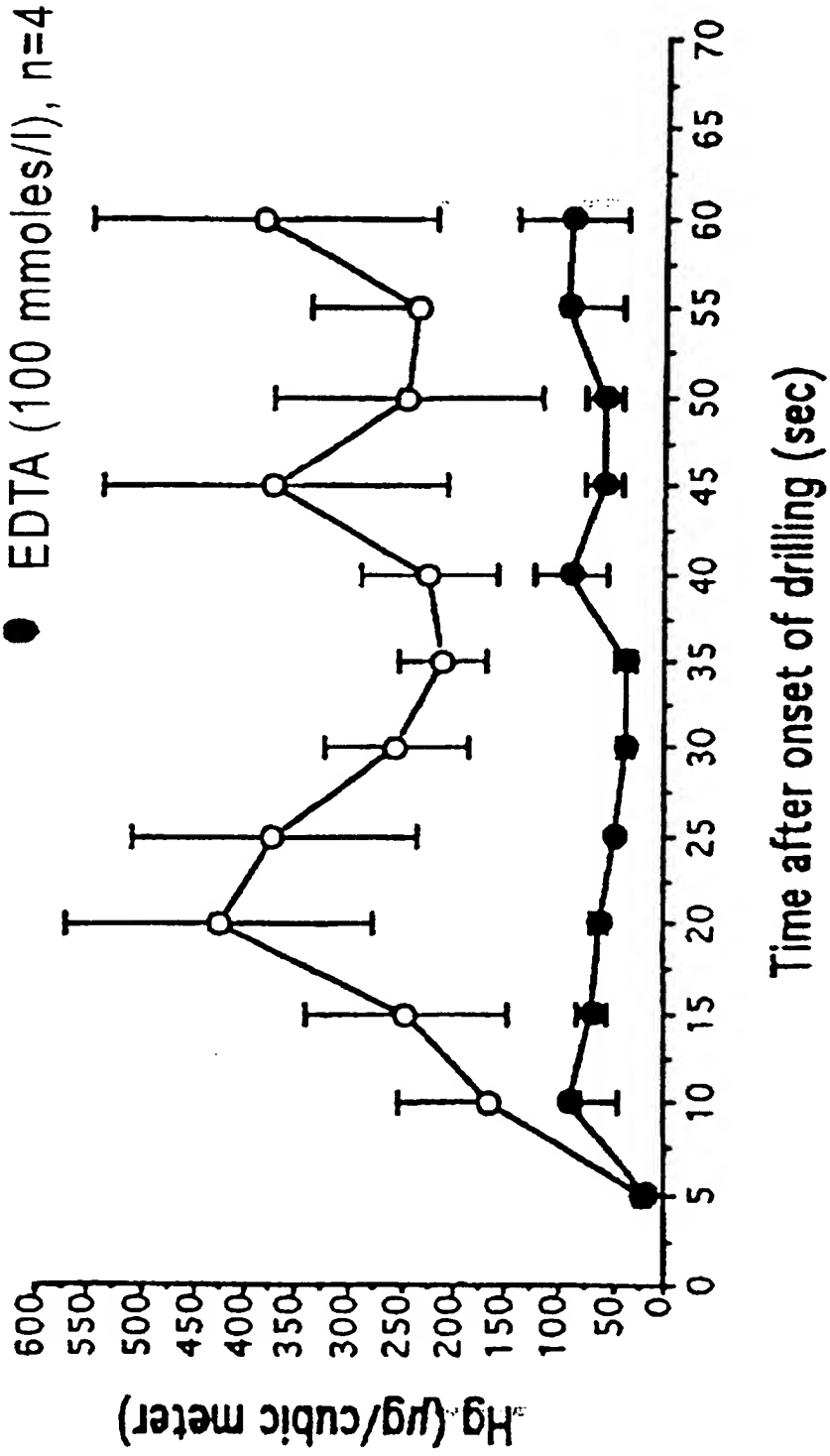
7. The composition of claim 6, c h a r a c t e r i z e d in that it contains an viscosity-modifying agent.

8. The composition of claim 6 or 7, c h a r a c t e r i - z e d in that said viscosity-modifying agent is carrageenan or carboxymethyl cellulose.

9. The composition of claim 6-8, c h a r a c t e r i - z e d in that its pH is from 5.0 to 8.5.

10. Use of EDTA, a salt of EDTA or another agent having high affinity for Hg^{2+} but not for Hg^{0} for the manufacture of a medicament for prevention of uptake of elementary mercury by the human body.

Fig. 1 In-vitro drilling model with constant perfusion



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01548

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 6/00, A61K 7/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9523584 A1 (LANGWORTH, SVEN), 8 Sept 1995 (08.09.95), abstract ---	1-10
A	WO 8000057 A1 (DENTAL THERAPEUTICS AB), 24 January 1980 (24.01.80) --- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jack Hedlund Telephone No. +46 8 782 25 00

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9523584	08/09/95	EP-A- 0710205	08/05/96
		EP-A- 0748206	18/12/96
		FI-A- 960330	24/01/96
		NO-A- 960345	26/01/96
		SE-A- 9400714	03/09/95
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		AU-A- 4805179	20/12/79
		CA-A- 1117020	26/01/82
		DE-C- 2952879	19/07/90
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